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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,613	01/30/2006	Richard G Vile	07039-444US1	6311

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EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 11/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/533,613	VILE ET AL.	
	Examiner	Art Unit	
	Kelaginamane T. Hiriyanna	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/23/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,5,11 and 23-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *2,5,11 and 23-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/29/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 8/23/2006 in response to office action mailed on 05/05/2006 has been acknowledged.

Claims 1, 3, 4, 6-10, and 12-22 have been cancelled.

Claims 2, 5, and 11 have been amended.

Claims 23-28 have been newly added.

Claims 2, 5, 11 and 23-28 *are pending and are examined in this office action. Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is* ***571-273-8300.***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 112

(I). Rejections of claims *1-22* under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement are here by withdrawn in view of applicants cancellation of claims and amendments to previous claims and further in view of the new rejection of the instant claims as below.

(II). Claims 23-25, 27-28, 33-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The scope of invention as claimed encompasses making any viral vector comprising a nucleic acid encoding a therapeutic peptide operably linked to any and/or

all heterologous destabilizing elements, all elements that are responsive to any inflammatory mediators or radiation or stabilized in proliferating cells and responsive to RAS activated pathway.

At best the specification teaches an adenoviral vector with a E1A protein coding sequences that is operably linked to a sequence encoding 3' UTR of cyclooxygenase-2 mRNA (Ad-E1A-COX), wherein the vector when introduced into target cells expressing RAS protein exhibit an enhanced stabilization and translation of the transcripts of said therapeutic coding sequences relative to cells that do not express RAS protein. The specification further only broadly describes a few other mRNA destabilizing sequences from TNF-alpha gene, urokinase plasminogen activator receptor gene, and VEGF gene and further mentions several viral vectors (e.g., vaccinia virus vector) only in passing.

Applicant is referred to the guidelines for ***Written Description Requirement*** published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110 (see <http://www.uspto.gov>). The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In analyzing whether the written description requirement is met for the genus claim, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e conserve motifs or domains). According to these facts, one skilled in the art would conclude that applicant was not in the possession of the claimed genus because a description of even a single member of this genus would not be representative of other nucleic acid constructs genus and is insufficient to support the claim.

(III). Rejections of claims *1-22* under 35 U.S.C. 112, first paragraph (enablement), are here by withdrawn in view of applicants cancellation of claims and amendments to previous claims and further in view of the new rejection of the instant claims as below.

(IV). Claims 2, 5, 11, 23-25, 27-28, 29, 33-34 and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vector and a method of introduction of a vector into a cell in vitro or into a cell in an experimental animal with an oncolytic adenoviral vector with a E1A protein coding sequences that is operably linked to a sequence encoding 3' UTR of cyclooxygenase-2 mRNA, wherein said vector was introduced by direct injection to the site of tumor, does not enable introducing any human cell in vivo with any viral vector, with any heterologously derived mRNA destabilizing sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. At the best the specification as filed is found only enabled for a method of gene therapy for treating treating a glioma in with an oncolytic adenoviral vector with a E1A protein coding sequences that is operably linked to a sequence encoding 3' UTR of cyclooxygenase-2 mRNA, wherein said vector was introduced by direct injection to the site of tumor.

Because of the lack of sufficient number of working examples, insufficient guidance and direction provided by Applicant, the inherent unpredictability of the art, and the nature of the invention, one of skill in the art would be required to perform a large amount of experimentation to make and/or use the invention in its full scope as claimed by Applicant. Such experimentation would be required to determine the types of vectors that could be used, the tissues tumors that could be treated, and the types of promoters that would produce enough protein for a long enough period of time to effect safe treatment. Further these claims are not enabled because one of skilled in the art, at the date of filing, would not be able to rely upon the state of the art in order to successfully predict a priori the in vivo effects of claimed gene transfers in a subject. Accordingly, in view of the lack of teachings in the art or guidance provided by the specification with regard to an enabled use of a method for safe treatment of a any and/or all tissue tumors by genetherapy, it would have required undue experimentation for one of skill in the art to make and use the full scope of the claimed invention

(V). Claims 29-32 and 35-37 are objected to because of dependence on rejected claims.

Claim Rejections - 35 USC § 102

(VI). Claims 23, 30-31, 33 and 34-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Risau et. al., (*WO 98/56936*; 12/17/1998).

The above claims are directed to a viral vector comprising a therapeutic polypeptide coding sequence that is operably linked to a heterologous destabilizing element that enhances the expression of said polypeptide in target cells including tumor cells

Regarding claims 23, 30-31, 33 and 34-35 Risau teaches compositions of recombinant viral vectors including adenoviral and retroviral vectors for gene therapy of tumors etc., (abstract, p.1, and p.18, 2nd paragraph) comprising therapeutic polypeptide coding sequences (p.11, 2nd paragraph bridging p.12, 1-2ndparagrph) with heterologous regulatory sequences derived from 3' untranslated region of vascular endothelial growth factor (VEGF) gene (abstract, p.1 and entire document) and wherein which said regulatory sequences are involved in hypoxia- regulated modulation (expression) of the therapeutic gene in target cells (p.5, 2nd paragraph). Regarding claim 22 Risau teaches hypoxia-mediated expression of the cloned genes with said regulatory elements in tumors of syngenic Fischer 344 rats (p.34, 2nd paragraph). The cited art anticipates the invention as claimed.

Claim Rejections - 35 USC § 103

(VII). Claims 2, 5, 23, 26-27, and 33-35 are rejected under 35 USC § 103(a) as being unpatentable over Wang et al (1997, Cacer Res. 57:5426-33) in view of Liu et al (2000, Chinese Medicl Journal 113:167-171).

The above claims are directed to a viral vector comprising a therapeutic polypeptide coding sequence that is operably linked to a heterologous destabilizing element wherein said heterologous destabilizing element is the 3' untranslated region of

the TNF-α gene that enhances the expression of said polypeptide in target cells including tumor cells.

Regarding claims 2, 5, 23, 26-27, and 33-35 Wang teaches vector constructs wherein 3' UTR of the human TNF-α gene encompassing the mRNA destabilizing element was operably linked to luciferase reporter constructs and transfected into human breast carcinoma cell lines that over express TNF-alpha. The inserted 3' UTR markedly and quantitatively suppressed the luciferase activity. Increased levels of luciferase activity were observed 3 hr after TNF-alpha stimulation of ZR-75-1 cells transfected by constructs containing AU-rich repeats. Wang concludes that AU rich repeats in the 3'UTR of human TNF-α mRNA may regulate gene expression in human epithelial cancer cells (Abstract). Wang however, does not teach the use of nucleic acid encoding a therapeutic polypeptide.

Liu teaches a viral vector used for transfecting murine breast tumor cells wherein IL2 gene, coding for a therapeutic polypeptide, is operably fused with TNF-alpha gene. The treated cells possessed lower tumorigenicity. Liu concludes the IL2-TNF-α fusion gene in concert act to improve their antitumor effectiveness.

Thus it would have been obvious for one of ordinary skill in the art to modify the vector of Wang by substituting the luciferase gene with a therapeutic gene in view of Liu and use the viral vector wherein an operable fusion of TNF-α gene or its 3'UTR region with a heterologous gene coding for a therapeutic polypeptide and use the compositions for transducing cancer cells as taught by Wand and Liu. One of skilled in the art would be motivated to do so as the 3'UTR elements of TNF-α selectively stabilize and modulate the expression of the therapeutic gene in a target cell as opposed to a non-target cell. One of ordinary skill in the art would have reasonable expectation of success of making and using viral vectors with 3'UTR elements of tumor necrosis factor gene operably fused with a therapeutic gene for treating tumor because of the teachings of teachings in the art. Thus, the claimed invention was *prima facie* obvious.

(VIII). Claims 27-29, 36-37 are rejected under 35 USC 103 (a) as being unpatentable over Risau et. al., (*WO 98/56936*; 12/17/1998) as applied to claims 23, 30-

31, 33 and 34-35 as above and further in view of Sheng et al (2000, J. Biol. Chem. 275:6628-6635) and Curiel et al (2000, Clinical Cancer. Res. 6:3395-3399).

The above claims are directed to a viral vector comprising a therapeutic polypeptide coding sequence that is operably linked to a heterologous destabilizing element that enhances the expression of said polypeptide in target cells including tumor cells

Regarding claims 23, 29-31, and 33-36 *Risau* teaches compositions of recombinant viral vectors including adenoviral and retroviral vectors for gene therapy of tumors etc., (abstract, p.1, and p.18, 2nd paragraph) comprising therapeutic polypeptide coding sequences (p.11, 2nd paragraph bridging p.12, 1-2ndparagrph) with heterologous regulatory sequences derived from 3' untranslated region of vascular endothelial growth factor (VEGF) gene (abstract, p.1 and entire document) and wherein which said regulatory sequences are involved in hypoxia- regulated modulation (expression) of the therapeutic gene in target cells (p.5, 2nd paragraph). Regarding claims Risau teaches hypoxia-mediated expression of the cloned genes with said regulatory elements in tumors of syngenic Fischer 344 rats (p.34, 2nd paragraph). However, *Risau* does not teach cyclooxygenase-2 gene 3' UTR sequences as destabilizing elements, its stabilization in proliferating cells or its responsiveness to RAS and P-MAPK activity and conditionally replicative Adenovirus.

Regarding claims 28-29, Sheng teaches regarding the use of 3'UTR sequences of cyclooxygenase-2 and regulation of gene expression in vector constructs where in which said sequences are operably included (abstract, p.6629, col.1-2). Sheng further teaches that inclusion of COX-2 3' UTR sequences in said constructs cause stabilization and induction of the heterologous gene (luciferase gene) in H-Ras induced cells (p.6631 col.1-2). Art teaches Ras oncogene is induced in proliferating cells for example in cancer cells (p.6634, col.3 and 3 rd paragraph).

Regarding E1A protein Curiel teaches regarding the development of a conditionally replicative Adenovirus for cancer therapy (p.3395, abstract). Curiel further teaches engineering of specificity conditionality of replication is based on tumor biology,

based on transcriptional control especially of E1A gene in various cancer cells (p.3396-97)

Thus it would have been obvious for one of ordinary skill in the art to operably modify adenviral vector constructs of Risau to have E1A gene under cyclo-oxygenase 2 gene 3'UTR mRNA destabilizing elements for treating tumors. One skilled in the art would be motivated to use of viral vectors comprising the 3'UTR elements to conditionally stabilize mRNAs coding for therapeutic peptides (e.g. cytotoxic or lytic genes) genes in selectively cancer cells that express RAS gene but not in non dividing normal cells adding to the safety of the vector system in treating cancer. One of ordinary skill in the art would have reasonable expectation of success of making and using the viral vectors incorporating said 3'UTR elements for treating tumor because of the teachings of *WO 98/56936 and* Sheng and Curiel as above. Thus, the claimed invention was *prima facie* obvious.

(IX). Claims 11, 32 are rejected under 35 USC 103 (a) as being unpatentable over Risau et. al., (*WO 98/56936*; 12/17/1998) applied claims 23, 30-31, 33 and 34-35 as above and further in view of Montuori et al (2001, FEBS letters 508:379-384) and Curiel et al (2000, Clinical Cancer. Res. 6:3395-3399).

The above claims are directed to a viral vector comprising a therapeutic polypeptide coding sequence that is operably linked to a heterologous destabilizing element that enhances the expression of said polypeptide in target cells including tumor cells

Regarding claims 23, 29-31, and 33-36 *Risau* teaches compositions of recombinant viral vectors including adenoviral and retroviral vectors for gene therapy of tumors etc., (abstract, p.1, and p.18, 2nd paragraph) comprising therapeutic polypeptide coding sequences (p.11, 2nd paragraph bridging p.12, 1-2ndparagrph) with heterologous regulatory sequences derived from 3' untranslated region of vascular endothelial growth factor (VEGF) gene (abstract, p.1 and entire document) and wherein which said regulatory sequences are involved in hypoxia- regulated modulation (expression) of the therapeutic gene in target cells (p.5, 2nd paragraph). Regarding claims Risau teaches

hypoxia-mediated expression of the cloned genes with said regulatory elements in tumors of syngenic Fischer 344 rats (p.34, 2nd paragraph). However, *Risau* does not teach UPAR mRNA destabilizing sequences

Montuori teaches regarding claims 11 and 32 of the use of post-transcriptional regulation of UPAR by UPA and teaches by reference the up-regulation of UPAR in several cancer cells and further specific sequences of UPAR are involved in the regulation (Abstract, p.379, and p.383-384).

Thus it would have been obvious for one of ordinary skill in the art to operably modify vector constructs of Risau to have a therapeutic gene under the control UPAR mRNA destabilizing elements for treating tumors. One skilled in the art would be motivated to use of viral vectors comprising the 3'UTR elements to conditionally stabilize mRNAs coding for therapeutic peptides (e.g. cytotoxic or lytic genes) genes in selectively cancer cells that express UPAR mRNA stabilizing functions (e.g., as in cancer cells). One of ordinary skill in the art would have reasonable expectation of success of making and using the viral vectors incorporating said UPAR mRNA destabilizing elements for treating tumor because of the teachings of *Risau and* Montuori as above. Thus, the claimed invention was *prima facie* obvious.

Conclusion:

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Friday from 9 AM-5PM. Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst *William N. Phillips* whose telephone number is ***571 272-0548.*** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Dave Nguyen*, may be reached at **(571) 272-0731.** The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status

of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

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